1* European CF survey: a concerted action on the identity and frequency of CFTR gene mutations among Turkish and North-African CF patients in Europe

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Background: Mutation spectra of the CFTR gene vary between populations. Knowledge of these mutation spectra is needed for diagnostic purposes, for counselling in CF families and for screening, either neonatal to improve prognosis, or preconceptional and prenatal to provide for reproductive options. There is only limited knowledge about the mutation spectra in migrant populations in Europe.
Aims: To determine the identity and frequency of mutations found in Turkish and North-African CF patients and to determine the test-sensitivity of common CF-gene mutation panels when offering carrier screening to Mediterranean people.
Methods: In a survey among 373 European CF-centres, we asked which mutations have been found among Turkish and North African CF patients.
Results: Fifty mutations had been found on 75.2% (95% CI: 70.4–80.0%) of CFTR alleles of patients (n = 156) originating from Turkey or North Africa. The mean sensitivity of common CF-gene mutation panels to detect these mutations was 50.6% (95% CI: 45.0–56.2%), and differed significantly between Turkish and North-African people: 41.7% (95% CI: 34.7–48.6%) versus 66.4% (95% CI: 57.7–75.2%). A sensitivity of 63.6% (95% CI: 58.2–69.0) can be achieved by expanding the mutation panels with these Mediterranean mutations.
Conclusion: A low test-sensitivity of common CF-gene mutation panels for carrier screening of Mediterranean people was observed. This raises questions on whether and how to implement CF-carrier screening in a multi-ethnic society.

2 A novel homozygous CFTR mutation in a Chinese man with infertility

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Aims: To describe a case of atypical cystic fibrosis in a Chinese male and review a rare CFTR mutation.
Methods: A 43 year-old Chinese male never smoker presented with his wife to the Infertility Clinic. He had never fathered any children. He was found to have apparent congenital bilateral absence of the vas deferens (CBAVD) with severe oligospermia (sperm concentration 0.6 million, volume 3.3 ml, morphology 12% normal). He was otherwise well with no past medical history. He had no respiratory symptoms. There was no family history of cystic fibrosis or any other respiratory disorder but there was a family history of thalassemia minor. His chest radiograph and pulmonary function tests were all normal. Oxygen saturation on room air was normal at 98%. His sweat chloride test was normal at 32 mmol/L.
Results: Genetics testing revealed homozygosity for an exon 11 transition mutation changing A to G at position 1798. This yielded an amino acid substitiution at position 556 with Valine replacing the normal Isoleucine residue.
Discussion: This is the first reported case of a homozygosity for the p.I556V mutation. This mutation has been reported in 2 other patients in a heterozygous state. Ghanem (1992) reported a 45 year-old fertile male with moderate pulmonary symptoms and a positive sweat chloride and a I556L/R31C mutation. While CFTR gene mutations are not common in Asians, there is growing evidence of cystic fibrosis in this population. However, it is felt that the mutation spectrum of CFTR in CBAVD may be different than the Caucasian population (Wong LJ et al, Hum Reprod, 2005). It is important to consider atypical cystic fibrosis in men presenting with infertility and evaluate for alternative mutations in the non-Caucasian population.

3 L138ins mutation of CFTR gene in CF patients from Russia

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The aim was to describe a variety of clinical phenotype of L138ins mutation (consequence insertion of leucine at 138 in Exon 4) in Russian CF patients.
Methods: molecular genetic identification (sequence of exon 4), evaluation of clinical status, sweat test values (ST), chest X-ray, sputum bacterial colonisation.
Results: 1997–2005 we found 5 subjects compound heterozygous for L138ins mutation and other CF mutations. The frequency of L138ins mutation is 0.8% of all mutant alleles of CFTR gene in Russia. Median (M) age at date of diagnosis of CF – 8.6 years [0.2–16 yr]. 2 patients (F508del/L138ins) were diagnosed before 5 months. 1 (2184insA/L138ins) – after 10 years and 2 (CFTRdele2,3(21kb)/L138ins) – after 16 years. M age at 01.2006 was 9.6±5.64 yr [16;3.2]. M level of ST was 90.5 mmol/l [64.8;119.5]. M Wt%/Ht% 92.5% [85;110%] before the treatment. 3 patients have mainly bronchopulmonary manifestation of the disease: cough from 1–1.5 months, bronchopulmonary exacerbations 2–3 times in year, requiring antibiotics treatment. 2 of these patients (2184insA/L138ins and CFTRdele2,3(21kb)/L138ins) have athelectasis of median lobe, they also have atopy (bronchial asthma, allergic bronchopulmonary aspergillosis,recurrent sinusitis and drug intolerance). 3 patients are on a low dose of pancreatic enzymes, and 1 (2184insA/L138ins) has a normal level of faecal elastase1 507.1 μg/l. 4 patients have biliary dyskinesia (2 of them have cholelithiasis). All patients have chronic colonization of St. aureus, 2 – Ps.aeruginosa, 1 – Candida sp.
Conclusion: It should be proposed that L138ins mutant CFTR protein conserves a residual activity. This fact may impact on the better prognosis of CF patients with this mutation in CF genotype (at least, in heterozygous status of such severe mutations as F508del, CFTRdele2,3(21kb), 2184insA).

4 Molecular identification of complex alleles in the CFTR gene

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The molecular diagnosis of Cystic Fibrosis is based on the genotype characterization by the CFTR gene mutation screening. More than 1400 mutations related with CF disease have been described. Substantial variation in the many aspects of CF phenotype among individuals bearing the same genotypes emphasizes the role of genetic background and environment. The different clinical expressions could be related to the presence of some complex alleles, since many CF mutations, associated to the most severe clinical features, have a wide expression incidence depending on the presence of an additional mild mutation in the same subject. The aim of this study was to analyze the frequency of complex alleles in the cohort of 27 classic CF patients followed at the CF Centre of Lombardy Region.
Molecular analysis of the coding regions, performed by DHPLC and automatic sequencing, allowed us to identify the follow complex alleles G542X/L1069R-L967S;DeltaF508/2183AA→G-V1153E;DeltaF508/W361R-R334L; DeltaF508/Y1032C-L137P; DeltaF508/S997F-R1438W, DeltaF508-A234D-I1027T. The inheritance of these complex alleles was confirmed by family studies involving parents, and, in some cases, grandparents.
Probably L1069R-L967S; V1153E; W361R-R334L, Y1032C-L137P, S997F-R1438W, A234D-I1027T in isolation should be considered as neutral variants but might significantly impair CFTR function when inherited in cis with another CFTR mutation. These data document the contribution of complex alleles to the wide phenotypic variability of CF.
Only functional expression studies of such complex alleles could elucidate their role in the pathogenesis of disease.

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